LETTERS

Managing the Diabetic Patient with Acute Myocardial Infarction

Professor Yudkin's article[1] perhaps makes it timely to ask whether, before the DIGAMI study[2] acquires the status of holy writ, we should go a little further in looking carefully at the subgroup analysis which those authors present. Yudkin rightly says that this analysis hints at a possible adverse effect of sulphonylureas. To my eyes a rather more fundamental point is that the subgroups who had been defined as having a high prior cardiovascular risk (groups 2 and 4) did not appear to derive any benefit whatsoever from intensive treatment with insulin. Since, as Dr Fisher points out,[3] the institution of tight glycaemic control in people with diabetes and myocardial infarction has substantial resource implications, it could be argued that we should confine the use of DIGAMI-style intensive treatment to those people who are, paradoxically, in the lower cardiovascular risk group since this is the only group for whom we have evidence of benefit.

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Managing the Diabetic Patient with Acute Myocardial Infarction: Author's Reply

The DIGAMI Study[1] showed an approximately 28 % reduction in deaths in diabetic patients treated with insulin–glucose infusion, followed by subcutaneous insulin for at least 3 months after discharge, after an acute myocardial infarction. Dr Fisken[2] raises the issue of sub-group analysis, suggesting that the benefits of intensive insulin therapy achieved statistical significance only in those patients in the study who were not previously treated with insulin and who were at low risk on the basis of age, previous cardiac history, and digoxin treatment. The argument goes that intensified treatment is necessary only in those not previously on insulin and who are at low risk, this providing some reduction in demands on overstretched resources.

I have previously argued the case against sub-group analysis in diabetic patients with cardiovascular disease.[3] If we had believed the sub-group analysis of the ISIS-2 study, we would not be giving aspirin to diabetic patients after myocardial infarction.[4] As the ISIS-2 authors point out, the lack of benefit of aspirin in that particular study was also seen by those born under the astrological signs of Gemini and Libra.[3,4] Subsequent studies have shown substantial benefits of aspirin in diabetic, as in non-diabetic, patients.[5] In the DIGAMI Study,[1] the benefits of intensified treatment were statistically homogeneous across all four sub-groups, suggesting that this may be a parallel phenomenon.

The other point, namely that of resource implication, is unpersuasive. The no previous insulin–low risk sub-group represents nearly half of all myocardial infarction patients, and another 35 % of the DIGAMI subjects were already on insulin, and therefore not likely to be treated without insulin after their infarct. Thus insulin treatment, intensified or not, is indicated in some 80 % of all patients, so any savings in terms of resources are likely to be pretty small.

Quite clearly, the DIGAMI Study needs confirming in larger numbers of patients, which might be possible with the results of the DIGAMI-2 Study. In the meantime, I stand by my contention[6] that we should be treating all diabetic patients with intensive insulin therapy indefinitely after a myocardial infarction.

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The Elusive Diagnosis of Gestational Diabetes

Your Guest Editorial on 'The Elusive Diagnosis of Gestational Diabetes'[1] was comprehensive and well informed but may have confused some who still believe that the Pedersen hypothesis[2] provides the physiological basis for understanding diabetic pregnancy. This proposed that maternal hyperglycaemia leads to stimulation of the fetal pancreas and hyperinsulinism, which is frequently manifest as large-for-dates babies and neonatal hypoglycaemia. It must therefore have disturbed many readers to discover that 'no relationship between maternal glycaemia, assessed at 28 weeks' gestation, and neonatal hypoglycaemia was seen in a large Canadian study of women with mild degrees of glucose intolerance'.[3] This finding is at variance with earlier work[4] in which the area under the 28 week oral glucose tolerance test in 31 women with normal or mildly impaired glucose tolerance was found to correlate inversely with the neonatal plasma glucose 2 hours after delivery $r = 0.69$, $p < .0001$). A similar correlation was found with the rate of glucose utilization during the first 2 hours after birth (incremental k value) and low neonatal plasma glucose levels were found to be associated with high plasma insulin levels.

The Canadian workers excluded women with gestational diabetes according to the National Diabetes Data Group criteria. Although this group defines abnormality on the basis of 0, 1, 2, and 3 h post-glucose values following a 50 g glucose load, it is possible to interpolate

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30′, 90′ and 150′ figures and deduce their cut-off point in terms of the area under the 3 h OGTT, which was the index of glucose tolerance used in the earlier work. This area is that of the figure generated by joining adjacent points of a 3 h OGTT with sampling every 30′, the units being mmol l^{-1}/0.5 h. The cut-off point is at an area of about 43.4 units. The earlier data,[5] also using a 50 g glucose load, showed that the 2 h post-natal blood glucose never fell to below 1.4 mmol l^{-1} if the 28 week 3 h OGTT area were less than 41.7 units. The Canadian workers did not use a single index of carbohydrate tolerance such as the area under the OGTT curve, despite the fact that this corrects, at least in part, for variations in gastric emptying rate and is probably the best single index of carbohydrate tolerance;[6] they rather looked at individual points in time, with no reference to the context in which they were estimated. Hypoglycaemia was defined as a baby requiring intravenous therapy, without any attempt at more precise physiological measurements. With this all-or-none definition, statistics could only be undertaken using a chi-square test rather than any form of correlation. The statistical results are difficult to evaluate because, despite reading the paper with great care, I am unable to discover the number of babies who required intravenous therapy for hypoglycaemia. If there were none, failure to demonstrate statistical significance would not be surprising.

I must conclude that the Pedersen hypothesis is still valid, and that the balance of scientific evidence still favours a correlation between maternal glucose intolerance and neonatal hypoglycaemia and hyperinsulinism.

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